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‘Approach to’ Concise Clinical Review

Approach to prolonged viral pneumonia in immunocompromised patients with COVID-19

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ABSTRACT

Incidence and clinical relevance: In immunocompromised patients, infection with SARS-CoV-2 may cause prolonged viral pneumonia. Due to limited clinical evidence, this phenotype is poorly addressed in guidelines and may therefore remain undiagnosed or inadequately treated.

Etiologies/ differential diagnosis: For clinical diagnosis of prolonged COVID-19 pneumonia, we propose the following diagnostic criteria: prolonged respiratory symptoms and/or fever beyond 30 days after symptom onset of COVID-19, in the presence of persistent radiologic features and persistently positive SARS-CoV-2 PCR and the absence of another apparent explanation. A negative PCR from the upper respiratory tract may not suffice to rule out prolonged viral pneumonia, as viral replication may be restricted to the lower respiratory tract. Alternative diagnoses should be considered in case of no response to empiric treatment. The differential diagnosis includes (co-)infection with a respiratory viral, bacterial or fungal pathogen, organizing pneumonia and other lung diseases.

Recommended treatment options and durations: In case of prolonged mild symptoms in combination with radiologic evidence and persistently positive SARS-CoV-2, we propose a 5- or 10-day course of antiviral treatment followed by antibody treatment as the primary treatment option. However, the availability of these drugs may be limited and effectiveness strongly dependent on the variant of SARS-CoV-2. Successful repeated or combination courses with antivirals have also been described.

Conclusion: Even though the phenotype of prolonged viral pneumonia in COVID-19 is described in literature, its epidemiology and mechanisms are still poorly understood. Therefore, our approach to this clinical problem is largely based on anecdotal evidence and expert opinion.

Incidence and clinical relevance

Immunocompromised patients are at increased risk for severe pulmonary infections, including severe COVID-19 [1]. In addition to severe disease, immunocompromised patients may also present with prolonged SARS-CoV-2 viral pneumonia [2,3]. For clinical diagnosis of prolonged COVID-19 pneumonia, we propose the following diagnostic criteria: prolonged respiratory symptoms and/or fever beyond 30 days after symptom onset of COVID-19, in the presence of persistent radiologic features and persistently positive SARS-CoV-2 PCR and the absence of another apparent explanation.

Prolonged viable shedding is common among immunocompromised patients, with a median of 4 weeks in a cohort of patients who were immunocompromised due to a hematologic malignancy or transplantation [4]. Prolonged viral shedding is also relatively common among people living with HIV with low CD4 counts and among kidney transplant patients [5,6]. In contrast, persistent infection is rare among healthy individuals. In a large community-based surveillance study performed in the United Kingdom, at least 26 days between positive samples was observed in 381 of 77,561 people (0,49 %) and at least 56 days in between positive samples was observed in 54 of 77,561 patients (0,07 %). Those with persistent infection had higher odds of persistent symptoms [7]. Furthermore, it has been demonstrated that persistent infection is associated with adaptive viral evolution within the host [8].

High age, male sex and common comorbidities are well-established risk factors for severe COVID-19. Among specific immunocompromised subgroups, especially patients with stem cell transplants within 2 years prior to COVID-19 are at risk for hospital admission, followed by those with recent solid organ transplant [1]. Prolonged viral shedding is common among patients with severe COVID-19 [9]. However, it remains un-

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clear to what extent prolonged viral pneumonia shares risk factors with severe COVID-19 as this condition is poorly addressed in large prospective studies.

Recently, we found that typical COVID-19 symptoms were present by day 30 of infection in 35 % and by day 90 in 18 % of patients with anti-CD20 treatment for any condition within 12 months before COVID-19. In these patients, prolonged COVID-19 respiratory and inflammatory symptoms were associated with prolonged PCR-positivity and changes in computed tomography [2]. The frequency of prolonged viral pneumonia in other immunocompromised groups remains unclear.

Despite the increased risk of complicated COVID-19 in immunocompromised patients, this group is insufficiently addressed in clinical trials. As a result, clinical guidance is least available in most complicated cases. Here, we aim to contribute to practice guidance in management of prolonged viral pneumonia in COVID-19, despite the poor availability of clinical evidence.

Clinical presentation

Typical COVID-19 symptoms related to viral pneumonia include shortness of breath, cough and fever. Even though other symptoms are common, during the infectious stage as well as post-infection, we do not consider them as primarily related to pneumonia for differential diagnostic purposes. Radiologically, COVID-19 pneumonia may appear as bilateral ground glass opacities with or without consolidation, often with a peripheral distribution, and most frequently involving the lower lobes [10]. Furthermore, an airway sample, either obtained from nasopharyngeal or oropharyngeal swab or from bronchoalveolar lavage (BAL), is typically positive for SARS-CoV-2 [2].

A negative PCR obtained from the upper respiratory tract may not be sufficient to rule out prolonged viral pneumonia can still be considered as viral replication may be restricted to the lower respiratory tract. For this purpose, as well as for the detection of possible other (co-)infections, BAL is preferred. Alternative diagnoses should be reconsidered in case of no response to empiric treatment.

Microbiology, immunology and pathogenesis

Research on prolonged symptoms related to COVID-19 infection (long COVID) has largely focussed on the general population and includes nonspecific symptoms, while viral persistence is considered one among several pathogenic mechanisms [11]. Even though several studies have observed immune dysregulation among long COVID patients, including T cell exhaustion, that could potentially explain viral persistence, these findings do not necessarily reflect the immune mechanisms involved in the specific case of prolonged viral pneumonia [11]. In fact, prolonged viral pneumonia did not correlate with long COVID symptoms after 26 weeks [7]. For clarity, we prefer to avoid the term ‘long COVID’ and its synonyms in patients with findings consistent with prolonged viral pneumonia.

Whereas immune disorders related to severe COVID-19 and long COVID are widely studied, the mechanisms responsible for persistent infection are still poorly understood. However, the available evidence is suggestive for an interplay between different immune mechanisms and cell lines. For instance, suppressed B-cell function in patients on anti-CD20 treatment results in inadequate humoral immune responses and decreased effectivity of vaccination. Among patients on anti-CD20 treatment, those with multiple sclerosis (MS) rarely developed prolonged viral pneumonia whereas this is a common condition among those with haematologic malignancy or connective tissue disease. In these patients, the underlying condition, age, comorbidities and/or (immunosuppressive) co-medications likely play a role beyond suppressed B cell function after anti-CD20 treatment [2]. Even when no anti-SARS-CoV-2-antibodies can be detected from the serum, T cell function may suffice in preventing severe COVID-19 [12]. It can be hypothesized that a robust T cell response may be sufficient to prevent prolonged viral pneumonia in a subset of patients with suppressed B cell function.

Thus, several mechanisms be affected in immunocompromised patients, depending on the underlying disease and immunomodulating effects of treatment.

Differential diagnosis and diagnostic work-up

Differential diagnosis includes (co-)infection with other respiratory viral, bacterial or fungal pathogens [13]. Testing for a panel of respiratory pathogens, preferably by BAL, should be considered especially in case of a negative PCR for SARS-CoV-2 obtained from the upper respiratory tract or if the response to antiviral treatment is not achieved in a sufficient period of time and in cases with severe or progressive disease. BAL is recommended in immunocompromised patients in the light of possible COVID-19 viral replication restricted to the lung, with negative samples from the upper respiratory tract, as well as possible other (opportunistic) infections or co-infections [14,15].

Organizing pneumonia after COVID-19 may present with similar imaging findings in the absence of molecular diagnostic findings, and this condition may respond well to treatment with corticosteroids [10]. The radiologic patterns found in COVID-19 may also be the result of other conditions such as pulmonary manifestation of underlying disease in patients with connective tissue disease. However, due to the similar clinical and radiologic presentation and the potentially harmful effect of corticosteroids in prolonged pneumonia, PCR re-testing of nasopharyngeal swabs for SARS-CoV-2 and other pathogens should be considered first in these patients, and reconsidered in the absence of a prompt response to corticosteroid treatment. Other conditions such as pulmonary haemorrhage, eosinophilic pneumonia, cardiogenic pulmonary oedema, interstitial lung disease and cardiogenic pulmonary oedema may also present with a similar clinical picture. BAL-fluid testing may be feasible to differentiate prolonged viral pneumonia from opportunistic coinfections or from some other conditions. The likelihood of prolonged viral pneumonia as well as alternative diagnoses may be highly dependent on the specific immune disorders of the patient.

Detailed history taking can provide essential clues in assessment of patients with prolonged viral pneumonia. These include medical history, timing of immunosuppressive medications, the number, type, and timing of vaccinations, previous COVID-19 episodes, and the qualitative assessment of onset, fluctuation and duration of symptoms, and response to medications. We propose that in immunocompromised patients, COVID-19 symptoms should be re-assessed at 1 month from onset.

Markers of inflammation, such as C-reactive protein (CRP), interleukin(IL)-6 and ferritin correlate with severity of COVID-19 [16]. However, compromised immunity and immunomodulatory treatment may affect the levels [17]. For instance, we observed a consistent and dramatic decrease of CRP short after treatment with IL-6 receptor antagonist tocilizumab, independent of clinical response to the treatment [18]. Patients with prolonged viral pneumonia may present with only mildly elevated CRP. Persistent respiratory and/or inflammatory symptoms is strongly associated with findings upon imaging and PCR-positivity consistent with prolonged viral pneumonia in immunocompromised patients [2]. Markers of interferon response such as myxovirus resistance protein A (MxA), monocyte chemoattractant protein-1 (MCP-1) or interferon (IFN)-y-induced protein 10 (IP-10) as well as other cytokines such as IL-6 and IL-10 may provide diagnostic clues, but their diagnostic value in prolonged viral pneumonia in COVID-19 has not been established [19]. Similarly, assessment of viral viability, PCR cycle threshold, sequencing and detection of antiviral antibodies and T cell function may be helpful in evaluation of the rel-

evance of the clinical findings and likelihood of prolonged COVID-19 pneumonia.

Recommended treatment and duration

Clinical evidence on treatment of prolonged viral pneumonia is largely limited to anecdotal evidence. Therefore, treatment is often based on expert opinion and on experiences shared by the scientific community.

Recently, we have published a retrospective study, in which several patients received a standard course of antiviral treatment (5 days of either remdesivir or ritonavir-boosted nirmatrelvir), directly followed by monoclonal antibody treatment directed at SARS-CoV-2. This led to a rapid and complete resolution of symptoms and other clinical findings in 5 of 6 mild cases without need for supplemental oxygen. However, this treatment was unsuccessful in hospitalized patients with respiratory support [2]. In case of prior treatment with high dose corticosteroids for clinical suspicion of organizing pneumonia, we aim to stop or reduce the dose of corticosteroids in order to optimize antiviral immunity before treatment.

Below, we will discuss several treatment options for COVID-19 in the light of immunocompromised patients.

Antiviral medications

Early treatment with antivirals such as remdesivir and ritonavir-boosted nirmatrelvir and is associated with significantly decreased risk of hospitalization for severe COVID-19 [20,21]. Due to their risk for complicated COVID-19, immunocompromised patients are likely to benefit from antiviral treatment. Therefore, immunocompromised patients should be instructed to seek immediate care or self-test in the case of symptoms suggestive of a respiratory infection, irrespective of the magnitude of symptoms. These patients may benefit of antiviral treatment also beyond the first week of infection. Beyond established antivirals, investigational agents (e.g. ensitrelvir) may also provide an option, for instance in patients not responding to remdesivir [22]. In many settings, prolonged courses of antivirals, for instance for 10 days, is common practice in immunocompromised patients instead of standard 5 day courses in immunocompetent patients. In prolonged infection, successful treatment with a combination of 2 or 3 antivirals and by repeated courses has been reported [23,24].

Neutralizing antibodies and convalescent plasma

Monoclonal and polyclonal neutralizing antibody therapies have been effective in preventing severe COVID-19, but high costs and limited availability have restricted the application of these treatments. A number of antiviral monoclonal antibodies, mainly but not exclusively targeting the receptor-binging domain of the spike glycoprotein of SARS-CoV-2, have been highly effective in prevention of severe COVID-19, especially in immunocompromised patients. However, the well-established treatments with for instance casirivimab/imdevimab or tixagevimab/cilgavimab are not anymore sufficiently effective in protection against circulating variants and their emergency use authorizations have been revoked [25]. The availability and applicability of neutralizing antibody therapy has changed during the COVID-19 era, and this will probably remain the case as new viral variants arise. We propose that immunocompetent patients should be prioritized for prevention with neutralizing antibody therapy, and that neutralizing antibody therapy should be made available as a treatment option for patients with prolonged viral pneumonia.

Transfusion of convalescent plasma has not been found effective in the treatment of severe COVID-19 in immunocompetent individuals, but a meta-analysis found that high-titre convalescent plasma decreases the risk of severe covid-19 in non-hospitalized patients. Furthermore, treatment with COVID-19 convalescent plasma is associated with mortality benefit for immunocompromised patients with COVID-19 [26]. Therefore, convalescent plasma could be feasible for preventive as well as for elective treatment in patients with compromised humoral immunity especially when antibody therapy is not available.

Interferon lambda

It has been demonstrated that higher interferon λ concentrations correlate with better recovery in severe COVID-19 due to its antiviral properties in combination with its anti-inflammatory effects. Although treatment with interferon I was not found feasible in COVID-19, a protective effect of interferon λ treatment was found to protect against complications in COVID-19 [27]. To date, effectiveness and safety of interferon λ in immunocompromised patients has not yet been assessed, but we consider this as an option worth experimentation within clinical trials.

Antithrombotics

While antithrombotic therapy with low-molecular weight heparin is recommended in noncritically ill, hospitalized immunocompetent patients based on findings from large trials, there is little evidence from specific immunocompromised patient groups [28]. We are not aware of any data disfavouring antithrombotic treatment in immunocompromised patients in general.

Access to specific medications

Access to specific treatments for COVID-19 may be limited by authorities to decrease the treatment costs of COVID-19 at the population level, or due to absence of sufficient knowledge of efficacy or side effects. In Finland, for instance, convalescent plasma treatment is not available. Furthermore, neutralizing antibody therapy with tixagevimab/cilgavimab was limitedly available to patients at increased risk for severe COVID-19, while treatment with monoclonal antibody AZD3152 was first made available for transplant patients exclusively while awaiting authorization for the use of this monoclonal antibody.

Prevention and closing knowledge gaps

Effectiveness of vaccination for COVID-19 is limited in immunocompromised patients, but this is highly dependent on the affected immunological pathways [29]. Intensive vaccination schedules are generally applied in immunocompromised patients, as immunity may rapidly wain. Furthermore, timed vaccination strategies of for instance 12 weeks before and 6 months after anti-CD20 therapy have been proposed, but differential duration of B cell depletion after anti-CD20 therapy and a paucity of research data limit the application of these strategies [30]. In general, we propose an intensive, heterologous and timed vaccination strategy on an individual basis. This implies a leading role for the treating specialist in the vaccination schedule of immunocompromised patients.

Conclusion

Prolonged viral pneumonia is not uncommon in immunocompromised COVID-19 patients. However, this phenotype remains poorly addressed in clinical trials. Because of the lack of data from clinical trials, guidance of management of COVID-19 in immunocompromised patients is limited. Thereby, this condition poses a huge challenge to these patients and their treating physicians. However, treatment with a combination of a standard course of antiviral medication followed by treatment with neutralizing antibodies may result in a rapid clinical response in a subset of patients.

With this perspective, we aim to provide some practical guidance in the management of COVID-19 in immunocompromised patients and prolonged viral pneumonia, despite the poor availability of clinical evidence.

SELF-QUIZ: right answers marked yellow

1) Which patient is likely at highest risk for hospitalization for COVID-19?.
   a) a 50-years old vaccinated woman with COVID-19 4 months after stem cell transplantation.
   b) an unvaccinated 65-year old man with COVID-19.
   c) a 50-years old vaccinated man with metastasized colon carcinoma.
   d) a person living with HIV and a CD4 count of 150 cells/mm^3.
2) In this manuscript, the authors propose diagnostic criteria for prolonged COVID-19 pneumonia. Which item is not part of their definition?.
   a) Persistent radiologic evidence of viral pneumonia.
   b) Respiratory symptoms or fever.
   c) The underlying immunodeficiency
   d) Molecular genetic testing.
3) In this manuscript, the authors propose treatment of prolonged COVID-19 pneumonia with a course of antiviral drug followed by neutralizing antibody treatment. What is the level of evidence behind this advice?.
   a) Systematic review and meta-analysis.
   b) Evidence from randomized controlled trials.
   c) Evidence from case-controlled studies.
   d) Anecdotal evidence from a case series and reports.
4) A specific group at risk for prolonged COVID-19 pneumonia is composed of patients on anti-CD20 drugs, which interfere with B cell function. Does this specific group benefit from vaccination?.
   a) Yes, because the humoral response to vaccination is unaffected, despite decreased B cell function in general.
   b) Yes. Robust T cell response can be detected after vaccination in these patients, even though the humoral response is often severely decreased.
   c) No. After registration of anti-CD20 medication, practically all protective immune responses vaccination are blocked.
   d) No. Vaccination should not be applied as this promotes dysbalanced immunity, which is associated with increased risk of COVID-19.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Thijs Feuth reports a relationship with Pfizer Inc that includes: speaking and lecture fees. Thijs Feuth reports a relationship with bioMérieux Inc that includes: consulting or advisory. Thijs Feuth reports a relationship with AstraZeneca that includes: consulting or advisory. Jarmo Oksi reports a relationship with Advanz Pharma Corp. that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Biocodex that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with GlaxoSmithKline Inc that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Medanets that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Pfizer that includes:. Jarmo Oksi reports a relationship with Professio that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Roche that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Tillotts that includes: speaking and lecture fees. Jarmo Oksi reports a relationship with Gilead Sciences Inc that includes: travel reimbursement. Jarmo Oksi reports a relationship with Unimedic Pharma AB that includes: travel reimbursement. Jarmo Oksi reports a relationship with AstraZeneca that includes: consulting or advisory. Jarmo Oksi reports a relationship with GlaxoSmithKline Inc that includes: consulting or advisory. Jarmo Oksi reports a relationship with MSD that includes: consulting or advisory. Jarmo Oksi reports a relationship with Pfizer that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Thijs Feuth: Writing – original draft, Conceptualization. **Jarmo Oksi:** Writing – review & editing, Supervision, Conceptualization.

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